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A Ready One-pot Preparation for Pyrrolo[2,1-*f*]-[1,2,4]triazine and Pyrazolo[5,1-*c*]pyrimido[4,5-*e*]-[1,2,4]triazine Derivatives

José Mª. Quintela,* María J. Moreira and Carlos Peinador

Departamento de Química Fundamental e Industrial, Facultad de Ciencias, Universidad de La Coruña. Campus de A Zapateira, E-15071, La Coruña, Spain.

Abstract: Several new 2,4-disubstituted pyrrolo[2,1-*f*][1,2,4]triazines and pyrazolo[5,1-*c*]-pyrimido[4,5-*e*][1,2,4]triazines are easily obtained from the reaction of *N*,*N*-dimethyldichloromethyleniminium chloride with 1-aminopyrrole-2-carbonitrile 1 and ethyl 4-amino-3-cyanopyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate 6, respectively.

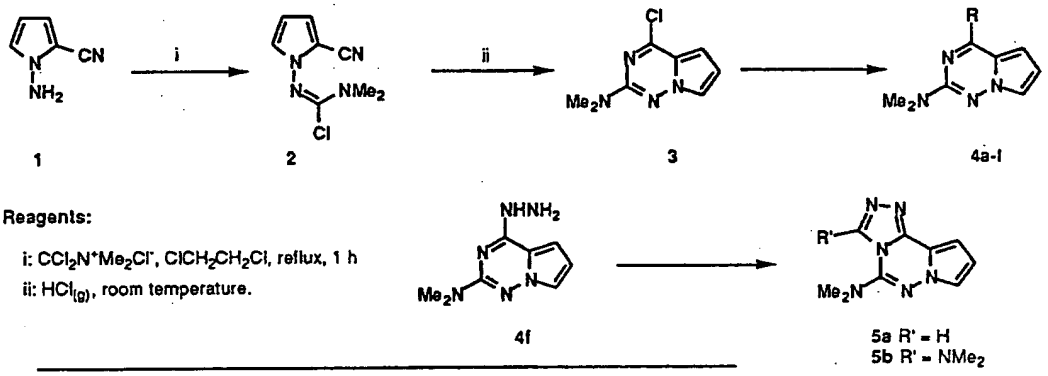
1,2,4-Triazines that are condensed with one or more heterocycles are well-known compounds and a wide variety of synthetic methods for their preparation are available. Compounds containing the 1,2,4-triazine moiety show biological activity and are found in natural materials. A large number of synthetic compounds containing the 1,2,4-triazine ring also have biological activity and are in use as pharmaceuticals, herbicides, pesticides, dyes, etc. The number of publications dealing with 1,2,4-triazines is high, particularly on account of their biochemical properties and various reviews dealing with their condensed ring systems have been published.[1]

There is a continuous widespread interest in the design and synthesis of novel purine-like C-nucleosides because of the potential biological activities associated with this system.[2] Recently, a simple synthetic approach, *via* the *N*-amination of 2-substituted pyrroles, to several 4-mono and 2,4-difunctionalized pyrrolo[2,1-*f*][1,2,4]triazine derivatives was reported.[3] Also, C-nucleosides incorporating the pyrrolo[2,1-*f*][1,2,4]triazine system are known[4] and the 4-aza-7,9-dideazaadenosine, a new cytotoxic synthetic C-nucleoside analogue of adenosine where the purine moiety is replaced by the pyrrolo[2,1-*f*][1,2,4]triazine ring, demonstrated a pronounced *in vitro* growth inhibitory activities against leukemic cell lives comparable to that of 9-deazaadenosine.[5] On the other hand, various pyrazolo[5,1-*c*][1,2,4]triazines have been synthesized by many research groups,[6] and some of them have been reported to possess biological activities such as antifungal[7] and tumor growth inhibitory[8] activities. The structural diversity and biological significance of fused pyrimidines have aroused much attention in the past few years owing to the wide range of biological activity of these compounds.[9] Many potential drugs have been modeled on them, particularly in cancer and virus research,[10] but few pyrazolo[5,1-*c*]pyrimido[4,5-*e*][1,2,4]triazines have been synthesized so far.[11]

The electrophilic character and structural diversity of methyleneiminium salts has ensured their prominent position in synthetic chemistry.[12] *N,N*-Dialkyldichloromethyleniminium chlorides (phosgeniminium chlorides) are known to be useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a dialkylamino group.[12] Reactions involving phosgeniminium chlorides and nucleophiles usually afford new electrophilic synthons such as amide chlorides, α-chloroenamines, 1,3-dichlorotrimethinecyanines, etc., which react further to produce, through either inter- or intra-molecular processes, various types of functionalized 5-, 6- and 7-membered ring systems.[13] In this context, some new methods for the preparation of polyheterocyclic compounds utilizing heterocyclic aminonitriles and phosgeniminium chloride have been developed in our laboratory.[14]

In our attempt to prepare heterocyclic compounds of biological interest and following our work on the synthesis, reactivity and physiological activity of polyheterocyclic systems which contain a pyrimidine moiety,[15] we found that pyrrolo[2,1-*f*][1,2,4]triazines **4**, congeners of substituted nucleic acid purines, and pyrazolo[5,1-*c*]pyrimido[4,5-*e*][1,2,4]triazines **9**, can now be readily prepared under mild reaction conditions, starting from the heterocyclic aminonitriles **1** and **6**, respectively, and *N,N*-dimethyldichloromethyleniminium chloride.

Scheme 1



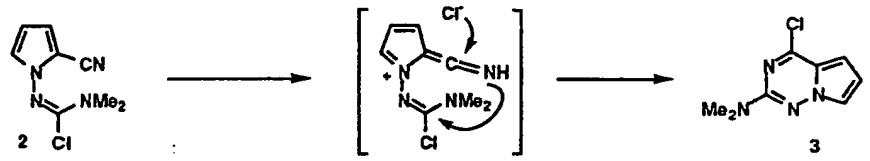
4	R	4	R	4	R
a	Piperidino	e	Butylamino	i	OC_6H_5
b	Morpholino	f	$NHNH_2$	j	OH
c	4-Benzylpiperazino	g	N_3	k	SH
d	*N*-4'-Acetylphenylpiperazino	h	OCH_2CH_3	l	SCH_3

The *N*-aminopyrrolonitrile **1**, used in this study was prepared *via* reaction of the commercially available pyrrole-2-carbaldehyde and hydroxylamine-*O*-sulfonic acid by a previously reported method.[3] On treatment with (dichloromethylene)dimethylammonium chloride in refluxing 1,2-dichloroethane, the *N*-aminopyrrolonitrile **1** afforded a mixture of the amide halide intermediate **2** and the 4-aza-7,9-dideazapurine **3** which were isolated by the concentration of the reaction mixture and purified by medium-pressure chromatography. Intermediate **2** underwent cyclization to the corresponding fused heterocyclic compound **3** *via* the reaction with dry hydrogen chloride. Direct one-pot synthesis using **1** and phosgeniminium salt in refluxing 1,2-dichloroethane for 1 h and subsequent treatment with hydrogen chloride provided the substituted

pyrrolo[2,1-*f*][1,2,4]triazine **3** in 75% yield. The structure of compounds **2** and **3** were determined from microanalyses and spectral data. The mass spectra showed the expected molecular ion peak and the IR spectrum of **2** exhibited a strong absorption band at $\nu = 1610\ cm^{-1}$ due to the imino group and presented the characteristic signal at $\nu = 2220\ cm^{-1}$ (CN), while the decoupled ^{13}C NMR spectrum showed one signal at $\delta =$ 113.3 due to the carbon atom in the one cyano group. After cyclization, the spectrum of compound **3** did not include those types of signals. The most salient features of the ^{1}H NMR and ^{13}C NMR spectra are given on Experimental.

Phosgeniminium salts are known to undergo condensation with CH-acidic compounds such as ketones, carboxylic acid and chlorides, nitriles and amides to give amide halides.[16] Amide chlorides have been similarly obtained from enamines,[17] fulvenes,[18] barbituric acid derivatives[19] and pyridopyrimidines[20] by reaction with dichloromethyleniminium salts. In addition, phosgeniminium salts do not react with the nitrile group unless it is sufficiently activated or the salts are previously transformed into chloroiminium chlorides by means of dry hydrogen chloride. Since the intermediate adduct **2** was isolated the reaction can be assumed to proceed as follows:[21]

Scheme 2



N,N-Dimethylguanine analogue **4j** and *N,N*-dimethyl-2-mercaptoguanine analogue **4k** were obtained by treatment of the bicyclic compound **3** with sodium hydroxide and sodium hydrosulfide, respectively. Similarly, nucleophilic displacement reaction of the chloride bearing group in the same key intermediate triazine **3** resulted in the formation on the corresponding substituted 4-aza-7,9-dideazapurine derivatives **4a-i**. The structures of these new compounds were also determined from microanalytical and spectral data. On treatment derivative **4f**, obtained by the reaction of **3** with hydrazine hydrate, with triethyl orthoformate and phosgeniminium chloride, cyclized to the annelated triazole ring **5a,b**, respectively. Compound **5a**, showed a signal at $\delta = 8.62$ in the ^{1}H NMR spectrum that was assigned to the H-3 hydrogen; also, its mass spectrum showed an intense peak at m/z = 202 corresponding to the molecular ion. Complete information about the NMR, IR and mass spectra is presented in the Experimental.

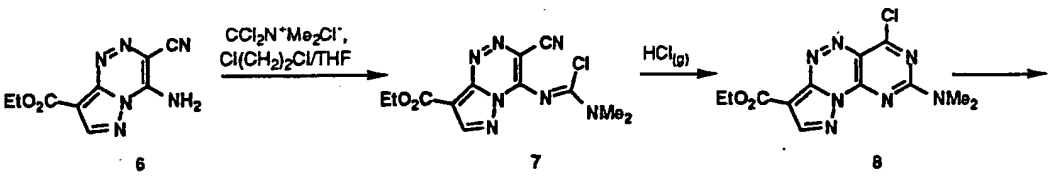
This is the first example, to our knowledge, of the annelation of a triazine ring to an existing heterocyclic aminonitrile using phosgeniminium chloride in which the amino moiety of the aminonitrile system is directly linked to a nitrogen atom. This synthetic approach may be useful in view of the biochemical interest in this compound class and shows that the reaction of *N*-aminopyrrolonitrile with (dichloromethylene)-dimethylammonium chloride provides a new, general route to 2,4-difunctionalized pyrrolo[2,1-*f*][1,2,4]-triazine (4-aza-7,9-dideazapurine) derivatives.

Similarly, the reaction of the ethyl 4-amino-3-cyanopyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate **6**[22] with phosgeniminium chloride gave **7** (Scheme 3). Amide halide intermediate **7** underwent cyclization to the corresponding fused compound **8** by reaction with dry hydrogen chloride. On treatment with phosgeniminium salt in refluxing 1,2-dichloroethane/THF for 1 hour and a subsequent treatment with hydrogen chloride, **6**

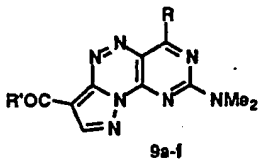
directly afforded the substituted fused heterocyclic compound **8** which, in turn, showed the remarkable reactivity of its chloro substituent towards nucleophilic agents. The structures of the new compounds were confirmed by elemental and spectroscopic features and are also summarized on Experimental.

In this simplicity, the affordability of the starting materials, good yields obtained and, straightforward product isolation, the proposed one-pot procedure compares favorably with other synthesis for the 4-aza-7,9-dideazapurine and the pyrazolo[5,1-*c*]pyrimido[4,5-*e*][1,2,4]triazine ring systems.

Scheme 3



6 7 8



9a-f

9	R	R'	9	R	R'
a	4-Phenylpiperazino	OCH_2CH_3	d	4-Piperidinopiperidino	OCH_2CH_3
b	4-Benzylpiperazino	OCH_2CH_3	e	Piperazino	OCH_2CH_3
c	*N*-4'-Acetylphenylpiperazino	OCH_2CH_3	f	$NHCH_2CH_2CH_3$	$NHCH_2CH_2CH_3$

EXPERIMENTAL PART

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on a VG Quattro spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for medium-pressure chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

1-Chlorodimethylaminomethylenaminopyrrole-2-carbonitrile (2):

A solution of **1** (1.10 g, 10 mmol) and phosgeneiminium salt (2.0 g, 12 mmol) in 1,2-dichloroethane (30 ml) was heated at reflux for 1 h. The solvent was removed under reduced pressure and the resulting solid was purified by MPLC using a gradient of eluents [hexane/ethyl acetate (9:1 to 6:1 v/v)] to obtain **3** (0.50 g, 25%) and **2** (1.38 g, 69%) as slightly yellow oil. IR (film): 3120; 2880; 2220 (CN); 1610. ^1H NMR δ ($CDCl_3$): 3.15 (s, 6H, NMe_2); 6.05 (t, 1H, J = 3.6 Hz, H-4); 6.64 (d, 2H, J = 3.6 Hz, H-3, H-5). ^{13}C NMR δ ($CDCl_3$): 40.4 (NMe_2); 102.2 (C-2); 107.0, 117.0, 124.0 (C-3, C-4, C-5); 113.3 (CN); 152.0 (C-Cl). MS (DEI): 198 (M^++2, 23); 196 (M^+, 68); 70 (100); 44 (51). Anal. Calcd. for $C_8H_9N_4Cl$: C, 48.90; H, 4.58; N, 28.54 . Found C, 48.76; H, 4.68; N, 28.40.

4-Chloro-2-dimethylaminopyrrolo[2,1-f][1,2,4]triazine (3):

Method A:

A solution of **1** (0.37 g, 3.5 mmol) and phosgeneiminium salt (0.68 g, 4.2 mmol) in 1,2-dichloroethane (30 ml) was heated at reflux for 1 h. A stream of dry hydrogen chloride was passed through the mixture for 3 h and the reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed under reduced pressure and the resulting solid was recrystallized from EtOH to afford **3** (0.50 g, 75%); mp 79-81 °C. IR (KBr): 3100; 1540. ^{1}H NMR δ ($CDCl_3$): 3.12 (s, 6H, NMe_2); 6.60 (dd, 1H, J = 4.6 Hz, J = 2.4 Hz, H-6); 6.73 (dd, 1H, J = 4.7 Hz, J = 1.6 Hz, H-5), 7.52 (dd, 1H, J = 2.4 Hz, J = 1.5 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 37.3 (NMe_2); 104.5, 111.8, 120.0 (C-5, C-6, C-7); 118.0 (C-4a); 153.2, 155.4 (C-2, C-4). MS (DEI): 198 (M^++2, 20); 196 (M^+, 83); 118 (100); 44 (91). Anal. Calcd. for $C_8H_9N_4Cl$: C, 48.86; H, 4.61; N, 28.49 Found C, 48.71; H,4.56; N, 28.65.

Method B:

A stream of dry hydrogen chloride was passed through a mixture of **2** (1.38 g, 7.0 mmol) in 1,2-dichloroethane (10 ml) for 3 h. The reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed under reduced pressure and the resulting solid was recrystallized from EtOH to obtain **3** (0.74 g, 55%).

2-Dimethylaminopyrrolo[2,1-f][1,2,4]triazines 4-substituted 4a-f; General Procedure.

A solution of **3** (0.5 mmol) and the appropriate amine (0.56 mmol) in EtOH (5 ml) was heated at reflux until all starting material had disappeared as checked by tlc. The solid obtained was then filtered off and recrystallized from EtOH.

2-Dimethylamino-4-piperidinopyrrolo[2,1-f][1,2,4]triazine ***4a*** (63%); mp 78-80 °C. IR (KBr): 3100; 2900. ^{1}H NMR δ ($CDCl_3$): 1.63-1.76 (m, 6H); 3.07 (s, 6H, NMe_2); 3.89-3.93 (m, 4H, NCH_2); 6.42 (dd, 1H, J = 4.5 Hz, J = 2.6 Hz, H-6); 6.56 (dd, 1H, J = 4.5 Hz, J = 1.5 Hz, H-5); 7.37 (dd, 1H, J = 2.4 Hz, J = 1.5 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 22.3, 25.8 (CH_2); 37.0 (NMe_2); 47.0 (NCH_2); 102.8, 107.9, 118.0 (C-5, C-6, C-7); 111.8 (C-4a); 154.1, 156.9 (C-2, C-4). MS (DEI): 245 (M^+, 100); 216 (31); 84 (64); 69 (81). Anal. Calcd. for $C_{13}H_{19}N_5$: C, 63.65; H, 7.80; N, 28.55. Found C, 63.44; H, 7.98; N, 28.60..

2-Dimethylamino-4-morpholinopyrrolo[2,1-f][1,2,4]triazine ***4b*** (60%); mp 92-94 °C. IR (KBr): 3100; 2980; 1570. ^{1}H NMR δ ($CDCl_3$): 3.07 (s, 6H, NMe_2); 3.79-3.85 (m, 4H, NCH_2); 3.93-3.99 (m, 4H, OCH_2); 6.45 (dd, 1H, J = 4.6 Hz, J = 2.5 Hz, H-6); 6.54 (dd, 1H, J = 4.6 Hz, J = 1.6 Hz, H-5); 7.40 (dd, 1H, J = 2.5 Hz, J = 1.4 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 37.2 (NMe_2); 46 (NCH_2); 66.7 (CH_2O); 102.9, 111.6, 118.4 (C-5, C-6, C-7); 108.6 (C-4a); 154.6, 157 (C-2, C-4). MS (DEI): 247 (M^+, 100); 190 (23); 92 (21). Anal. Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32. Found C, 58.47; H, 6.81; N, 28.40.

4-(4-Benzylpiperazino)-2-dimethylaminopyrrolo[2,1-f][1,2,4]triazine ***4c*** (64%); mp 122-124 °C. IR (KBr): 3100; 2960; 1580. ^{1}H NMR δ ($CDCl_3$): 2.57 (t, 4H, J = 5.1 Hz, NCH_2); 3.06 (s, 6H, NMe_2); 3.56 (s, 2H,

NCH_2Ph); 3.98 (t, 4H, J = 5.07 Hz, NCH_2); 6.44 (dd, 1H, J = 4.6 Hz, J = 2.4 Hz, H-6); 6.53 (dd, 1H, J = 4.6 Hz, J = 1.6 Hz, H-5); 7.26-7.40 (m, 6H, H-7, C_6H_5). ^{13}C NMR δ ($CDCl_3$): 37.2 (NMe_2); 45.6, 52.9 (NCH_2); 63.0 (NCH_2Ph); 103.0, 108.3, 118.3 (C-5, C-6, C-7); 111.8 (C-4a); 127.3, 128.3, 129.2, 137.7 (C_6H_5); 154.3, 157.0 (C-2, C-4). MS (DEI): 336 (M^+, 18); 190 (100); 91 (81). Anal. Calcd. for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98. Found C, 67.98; H, 7.23; N, 24.80.

4-(N-4'Acetylphenylpiperazino)-2-dimethylaminopyrrolo[2,1-f][1,2,4]triazine **4d** (66%); mp 156-158 °C. IR (KBr): 3100; 2940; 1600 (CO). ^1H NMR δ ($CDCl_3$): 2.53 (s, 3H, CO-CH_3); 3.08 (s, 6H, NMe_2); 3.53-3.60 (m, 4H, NCH_2); 4.13-4.19 (m, 4H, NCH_2); 6.47 (dd, 1H, J = 4.5 Hz, J = 2.5 Hz, H-6); 6.59 (dd, 1H, J = 4.5 Hz, J = 1.3 Hz, H-5); 7.42 (dd, 1H, J = 2.6 Hz, J = 1.5 Hz, H-7); 6.83, 7.90 (AA'XX' system, 4H, J = 9.0 Hz, $C_6H_4COCH_3$). ^{13}C NMR δ ($CDCl_3$): 26.1 ($COCH_3$); 37.2 (NMe_2); 44.8, 46.2 (NCH_2); 103.0, 108.6, 118.4 (C-5, C-6, C-7); 111.5 (C-4a); 112.6, 127.5, 130.4, 154.3 (C_6H_4); 153.3, 156.7 (C-2, C-4); 196.4 (CO). MS (DEI): 364 (M^+, 70); 190 (100). Anal. Calcd. for $C_{20}H_{24}N_6O$: C, 65.91; H, 6.64; N, 23.06. Found C,65.75; H, 6.58; N, 23.25.

4-Butylamino-2-dimethylaminopyrrolo[2,1f][1,2,4]triazine **4e** (71%); mp 88-90 °C. IR (KBr): 3300-3200 (NH) 2880; 1590. ^1H NMR δ ($CDCl_3$): 0.96 (t, 3H, J = 7.2 Hz, CH_2CH_3); 1.42 (m, 2H, CH_2CH_3). 1.65 (m, 2H, $CH_2CH_2CH_3$); 3.14 (s, 6H, NMe_2); 3.53 (q, 2H, J = 7.0 Hz, NCH_2); 5.14 (s, 1H, NH); 6.35-6.42 (m, 2H, H-6, H-5); 7.30 (dd, 1H, J = 2.2 Hz, J = 1.6 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 13.8 (CH_2CH_3); 20.1 (CH_2CH_3); 31.6 ($CH_2CH_2CH_3$); 37.2 (NMe_2); 40.1 (NCH_2); 97.6, 108.2, 117.8 (C-5, C-6, C-7); 111.8 (C-4a); 153.6, 157.6 (C-2, C-4). MS (DEI): 233 (M^+, 100); 93 (52). Anal. Calcd. for $C_{12}H_{19}N_5$: C, 61.77; H, 8.21; N, 30.02. Found C, 61.82; H, 8.34; N, 29.84.

2-Dimethylamino-4-hydrazinopyrrolo[2,1-f][1,2,4]triazine **4f** (72%); mp 220-222 °C. IR (KBr): 3310-3260 (NH, NH_2). ^1H NMR δ ($CDCl_3$): 3.12 (s, 6H, NMe_2); 4.16 (s, 2H, NH_2); 6.40-6.50 (m, 2H, H-6, H-5; 6.63 (s, 1H, NH); 7.35-7.44 (m, 1H, H-7). ^{13}C NMR δ ($CDCl_3$): 37.3 (NMe_2); 98.2, 108.7, 118.1 (C-5, C-6, C-7), 110.2 (C-4a); 155.3, 157.0 (C-2, C-4). MS (DEI): 192 (M^+,40). Anal. Calcd. for $C_8H_{12}N_6$: C, 49.99; H, 6.29; N, 43.72. Found C, 50.18; H, 6.27; N, 43.64.

4-Azido-2-dimethylaminopyrrolo[2,1-f][1,2,4]triazine (4g):

A solution of sodium azide (0.03 g, 0.56 mmol) in water (0.2 ml) was added to a solution of **3** (0.10 g, 0.5 mmol) in DMSO (2 ml) . The reaction mixture was stirred at room temperature for 4 h and water (20 ml) was then added. The solid formed was finally filtered off and recrystallized from EtOH to yield **4g** (0.07 g, 70%); mp 98-100 °C. IR (KBr): 3100; 2150 (N_3). ^1H NMR δ ($CDCl_3$): 3.13 (s, 6H, NMe_2); 6.51-6.61 (m, 2H, H-5, H-6); 7.48-7.51 (m, 1H, H-7). MS (DEI): 203 (M^+, 19); 84 (54); 69 (100). Anal. Calcd. for $C_8H_9N_7$: C, 47.29; H, 4.46; N, 48.25. Found C, 47.51; H, 4.39; N, 48.11.

2-Dimethylamino-4-ethoxypyrrolo[2,1-f][1,2,4]triazine (4h):

A solution of **3** (0.10 g, 0.5 mmol) and 35% NaOH (1 ml) in EtOH (1 ml) was heated at reflux for 30 min. The resulting solid was filtered off and recrystallized from EtOH to yield **4h** (0.07 g, 67%); mp 62-64 °C. IR (KBr): 3100; 2980. ^1H NMR δ ($CDCl_3$): 1.46 (t, 3H, J = 7.1 Hz, CH_2CH_3); 3.10 (s, 6H, NMe_2); 4.54

(q, 2H, J = 7.1 Hz, CH_2); 6.46 (dd, 1H, J = 4.4 Hz, J = 2.4 Hz, H-6); 6.62 (dd, H, J = 4.4 Hz, J = 1.6 Hz, H-5); 7.40 (dd, 1H, J = 2.2 Hz, J = 1.6 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_2CH_3); 37.2 (NMe_2); 62.0 (CH_2CH_3); 100.8, 109.3, 118.2 (C-5, C-6, C-7); 112.1 (C-4a); 156.6 , 160.7 (C-2, C-4). MS (DEI): 206 (M^+, 25); 149 (100). Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16 Found C, 58.42; H, 6.70; N, 27.29.

2-Dimethylamino-4-phenoxypyrrolo[2,1-f][1,2,4]triazine (4i):

A solution of **3** (0.10 g, 0.5 mmol), phenol (0.10 g, 1.2 mmol) and a catalytic amount of 10% KOH in THF (3 ml) was heated at reflux for 20 h. The solid formed was filtered off and recrystallized from EtOH to give **4i** (0.05 g, 40%); mp 100-102 °C. IR (KBr): 3100; 2800. ^{1}H NMR δ ($CDCl_3$): 2.94 (s, 6H, NMe_2); 6.55 (dd, 1H, J = 4.4 Hz, J = 2.4 Hz, H-6); 6.75 (dd, 1H, J = 4.6 Hz, J = 1.5 Hz, H-5); 7.22-7.51 (m, 6H, C_6H_5, H-7). ^{13}C NMR δ ($CDCl_3$): 37.0 (NMe_2); 102.0, 110.0, 119.0 (C-5, C-6, C-7), 111.6 (C-4a); 122.0, 125.4, 129.0, 152.0 (C_6H_5); 156.2, 160.6 (C-2, C-4). MS (DEI): 254 (M^+, 100); 225 (32), 167 (34). Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found C, 66.24; H, 5.67; N, 21.85.

2-Dimethylaminopyrrolo[2,1-f][1,2,4]triazin-4(3H)-one (4j):

Method A:

A solution of **3** (0.10 g, 0.5 mmol) and amonium acetate (0.12 g, 1.5 mmol) in acetic acid (1 ml) was heated at reflux for 4h. The solid formed was filtered off and recrystallized from EtOH to afford **4j** (0.06 g, 66%); mp 234-236 °C. IR (KBr): 3100 (NH); 1670 (CO). ^{1}H NMR δ ($CDCl_3$): 3.08 (s, 6H, NMe_2); 6.39 (dd, 1H, J = 4.4, J = 2.5 Hz, H-6); 6.80 dd, 1H, J = 4.4 Hz, J = 1.8 Hz, H-5); 7.24 (dd, 1H, J = 4.6 Hz, J = 2.3 Hz, H-7); 10.60 (s, 1H) ^{13}C NMR δ ($CDCl_3$): 38.2 (NMe_2); 107.4, 109.2, 120.8 (C-5, C-6, C-7), 116.0 (C-4a); 148.7 (C-2); 157.1 (C-4). MS (DEI): 178 (M^+, 100); 94 (46). Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found C, 54.00; H, 5.55; N, 31.56.

Method B:

A solution of **3** (0.20 g, 1.0 mmol) and a catalytic amount of 35% NaOH in DMSO (1 ml) was stirred at room temperatue for 12 h. The reaction mixture was poured into water (10 ml) and the solution neutralized with 2N HCl. The solid formed was purified by MPLC. Elution with hexane/AcOEt (10:1, v/v) afforded **4j** (0.06 g, 33%).

2-Dimethylaminopyrrolo[2,1-f][1,2,4]triazin-4(3H)-thione (4k):

$NaSHxH_2O$ (0.20 g) was added in portions to a solution of **3** (0.10 g, 0.5 mmol) in EtOH (5 ml). The reaction mixture was stirred at room temperature for 12 h. The solvent was removed at reduced pressure and water (10 ml) was added. The solution was neutralized with 2N HCl and the precipitate was filtered off to yield **4k** (0.095 g, 96%); mp 185-187 °C. IR (KBr): 3100; 1560. ^{1}H NMR δ ($CDCl_3$): 3.05 (s, 6H, NMe_2); 6.47 (dd, 1H, J = 4.6 Hz, J = 2.4 Hz, H-6); 7.17-7.20 (dd, 1H, J = 4.6 Hz, J = 1.6 Hz, H-5); 7.27 (dd, 1H, J = 2.7 Hz, J = 1.6 Hz, H-7); 9.22 (s, 1H). ^{13}C NMR δ ($CDCl_3$): 38.1 (NMe_2); 111.0, 112.4, 121.4 (C-5, C-6, C-7); 124.9 (C-4a), 146.6 (C-2); 174.6 (C-4). MS (DEI): 194 (M^+, 100), 149 (32); 110 (58); 69 (50). Anal. Calcd. for $C_8H_{10}N_4S$: C, 49.46; H, 5.20; N, 28.84. Found C, 49.64; H, 5.26; N, 28.68.

2-Dimethylamino-4-methylthiopyrrolo[2,1-f][1,2,4]triazine (4l):

15% KOH (1.2 ml) and methyl iodide (0.14 g, 1.0 mmol) was added to a solution of **4k** (0.13 g, 0.6 mmol) in acetone (12 ml) . The reaction mixture was stirred at room temperatue for 1 h. The solvent was removed at reduced pressure and water (10 ml) was added. The solid formed was filtered off and recrystallized from EtOH to afford **4l** (0.09 g, 64%); mp 92-94 °C. IR (KBr): 3100; 1560. ^{1}H NMR δ ($CDCl_3$): 2.62 (s, 3H, CH_3); 3.15 (s, 6H, NMe_2); 6.49 (dd, 1H, J = 4.6 Hz, J = 2.4 Hz, H-6); 6.59 (dd, 1H, J = 4.4 Hz, J = 1.5 Hz, H-5); 7.40 (dd, 1H, J = 2.4 Hz, J = 1.5 Hz, H-7). ^{13}C NMR δ ($CDCl_3$): 11.4 (CH_3), 37.2 (NMe_2); 101.0, 110.0, 118.2 (C-5, C-6, C-7), 117.8 (C-4a); 155.5, 163.0 (C-2, C-4). MS (DEI): 208 (M^+, 34), 149 (31); 69 (100). Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.90; H, 5.81; N, 26.90. Found C, 51.71; H, 5.98; N, 27.06.

5-Dimethylaminopyrrolo[2,1-f][1,2,4]triazolo[4,5-d][1,2,4]triazine (5a):

A solution of **4f** (0.12 g, 0.60 mmol) and a catalytic amount of *p*-toluensulfonic acid in triethyl ortoformate (1 ml) was heated at reflux for 3 h. The solid formed was filtered off and recrystallized from EtOH to afford **5a** (0.08 g, 63%); mp 158-160 °C. IR (KBr): 3100; 1540. ^{1}H NMR δ ($CDCl_3$): 3.04 (s, 6H, NMe_2); 6.58 (dd, 1H, J = 4.3 Hz, J = 2.8 Hz, H-9); 7.09 (dd, 1H, J = 4.4 Hz, J = 1.5 Hz, H-10); 7.42 (dd, 1H, J = 2.7 Hz, J = 1.6 Hz, H-8); 8.62 (s, 1H, H-3). ^{13}C NMR δ ($CDCl_3$): 41.2 (NMe_2); 104.0, 112.5, 119.8 (C-8, C-9, C-10); 110.0 (C-10a); 134.8 (C-3); 142.3, 144.4 (C-5, C-10b). MS (DEI): 202 (M^+, 100); 69 (81). Anal. Calcd. for $C_9H_{10}N_6$: C, 53.46; H, 4.98; N, 41.56. Found C, 53.60; H, 5.01; N, 41.40.

3,5-Di(dimethylamino)pyrrolo[2,1-f][1,2,4]triazolo[4,5-d][1,2,4]triazine (5b):

A solution of **4f** (0.18 g, 0.9 mmol) and phosgeniminium salt (0.18 g, 1.1 mmol) in 1,2-dichloroethane (10 ml) was stirred at room temperature for 1h. The solvent was removed at reduced pressure and the residue recrystallized from EtOH to give **5b** (0.12 g, 53 %); mp 183-185 °C. IR (KBr): 3100; 1590. ^{1}H NMR δ ($CDCl_3$): 2.97 (s, 6H, NMe_2); 3.12 (s, 6H, NMe_2); 6.59 (dd, 1H, J = 4.4 Hz, J = 2.6 Hz, H-9); 7.47-7.54 (m, 2H, H-8, H-10). ^{13}C NMR δ ($CDCl_3$): 41.9 (NMe_2); 43.1 (NMe_2); 108.6 (C-10a); 110.1, 112.2, 122.6 (C-8, C-9, C-10); 140.8, 142.1, 151.8 (C-3, C-5, C-10b). MS (DEI): 245 (M^+, 100); 201 (47); 149 (35). Anal. Calcd. for $C_{11}H_{15}N_7$: C, 53.86; H, 6.16; N, 39.97. Found C, 53.67; H, 6.21; N, 40.13.

Ethyl 4-chlorodimethylaminomethylenamino-3-cyanopyrazolo[5,1-c][1,2,4]-triazine-8-carboxylate (7):

A solution of **6** (0.20 g, 0.9 mmol) and phosgeniminium salt (0.17 g, 1.0 mmol) in dry 1,2-dichloroethane/THF (2:1, v/v, 30 ml) was heated at reflux for 1 h. The solvent was removed under reduced pressure and the resulting solid was purified by MPLC using hexane/ethyl acetate (6:1 v/v) as eluent to obtain **7** (0.23 g, 83%); mp 208-210 °C. IR (KBr): 3100; 2220 (CN); 1690 (CO). ^{1}H NMR δ ($CDCl_3$): 1.45 (t, 3H, J = 7.1 Hz, CH_2CH_3); 3.48 (s, 3H, NMe_2); 3.49 (s, 3H, NMe_2); 4.51 (q, 2H, J = 7.1 Hz, CH_2O); 8.67 (s, 1H, H-7). ^{13}C NMR δ ($CDCl_3$): 14.4 (CH_2CH_3); 41.7 (NMe_2); 61.3 (CH_2); 106.5 (C-8); 114.6 (C-3); 116.8 (CN); 142.7 (C-Cl); 148.2 (C-8a); 149.2 (C-7); 161.4 (CO). MS (DEI): 323 (M^++2, 5); 321 (M^+, 13); 249 (100). Anal. Calcd. for $C_{12}H_{12}N_7O_2Cl$: C, 44.80; H, 3.76; N, 30.47. Found C, 44.61; H, 3.69; N, 30.63.

Ethyl 6-chloro-8-dimethylaminopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate (8):

Method A:

A solution of **6** (0.81 g, 3.5 mmol) and phosgeniminium salt (0.68 g, 4.2 mmol) in dry 1,2-dichloroethane/THF (2:1, v/v, 60 ml) was heated at reflux for 1 h. A stream of dry hydrogen chloride was passed through a mixture for 3 h and the reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed under reduced pressure and the resulting solid was recrystallized from EtOH to afford **8** (0.52 g, 46%); mp 230-232 °C. IR (KBr): 2960; 1690 (CO). ^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H, J = 7.1 Hz, CH_2CH_3); 3.47 (s, 3H, NMe_2); 3.48 (s, 3H, NMe_2); 4.50 (q, 2H, J = 7.1 Hz, CH_2O); 8.66 (s, 1H, H-2). ^{13}C NMR δ ($CDCl_3$): 14.3 (CH_2CH_3); 38.3 (NMe_2); 38.4 (NMe_2); 61.3 (CH_2); 108.6 (C-3); 125.0 (C-5a); 143.0, 147.8 (C-3a, C-9a); 148.1 (C-2); 159.5, 161.5 (C-2, C-4); 164.8 (CO). MS (DEI): 323 (M^++2, 8); 321 (M^+, 21); 249 (100). Anal. Calcd. for $C_{12}H_{12}N_7O_2Cl$: C, 44.80; H, 3.76; N, 30.47. Found C, 44.78; H, 3.72; N, 30.50.

Method B:

A stream of dry hydrogen chloride was passed through a mixture of **7** (0.23 g, 0.7 mmol) in 1,2-dichloroethane/THF (2:1, 10 ml) for 3 h. The reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed under reduced pressure and the resulting solid was recrystallized from EtOH to obtain **8** (0.15 g, 65 %).

Ethyl 8-dimethylaminopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate 4-substituted 9a-e; General Procedure.

A solution of **8** (0.3 mmol) and the appropriate amine (0.35 mmol) in DMF (6 ml) was heated at reflux until all starting material had disappeared as checked by tlc (2-3 h). The solid obtained was then filtered off and recrystallized from $EtOH/CH_2Cl_2$.

Ethyl 8-dimethylamino-4-(4-phenylpiperazino)pyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate **9a** (86%); mp 249-250 °C. IR (KBr): 2980; 1710 (CO). ^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H, J = 7.1 Hz, CH_2CH_3); 3.33 (s, 4H, NCH_2); 3.38-3.45 (m, 10H, NMe_2, NCH_2); 4.52 (q, 2H, J = 7.1 Hz, CH_2O); 6.88-7.35 (m, 5H, C_6H_5); 8.62 (s, 1H, H-2). ^{13}C NMR δ ($CDCl_3$): 14.6 (CH_2CH_3); 37.6 (NMe_2); 37.8 (NMe_2); 46.8, 49.3 (NCH_2); 61.0 (OCH_2); 105.7 (C-3); 116, 120.2, 129.3 (C_6H_5); 123.0 (C-5a); 147.5 (C-2); 144.0, 150.6 (C-3a, C-9a); 157.4, 159.9; 162.2 (C-6, C-8, CO). MS (DEI): 447 (M^+, 14); 145 (40); 132 (100). Anal. Calcd. for $C_{22}H_{25}N_9O_2$: C, 59.05; H, 5.63; N, 28.17. Found C, 58.91; H, 5.75; N, 28.25.

Ethyl 4-(4-benzylpiperidino)-8-dimethylaminopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate **9b** (50%); mp 200-202 °C. IR (KBr): 2900; 1690 (CO). ^{1}H NMR δ ($CDCl_3$): 1.45 (t, 3H, J = 7.1 Hz, CH_2CH_3); 1.80-1.97 (m, 3H, CH_2, CH); 2.58 (d, 2H, J = 6.6 Hz CH_2-C_6H_5); 3.05-3.41 (m, 10H, NMe_2, NCH_2, CH_2); 4.50 (q, 2H, J = 7.1 Hz, CH_2O); 5.20 (br s, 2H, NCH_2); , 6.20 (br s, 2H, NCH_2); 7.13-7.33 (m, 5H, C_6H_5); 8.60 (s, 1H, H-2). ^{13}C NMR δ ($CDCl_3$): 14.5 (CH_2CH_3); 32.5, 32.6 (CH_2, CH_2-C_6H_5); 37.4 (NMe_2); 37.6 (NMe_2); 38.2 (CH); 42.8 (NCH_2); 61.0 (CH_2O); 105.3 (C-3); 122.7 (C-5a); 126, 128.2, 129.0

(C_6H_5); 139.8, 143.8 (C-3a, C-9a) 147.4 (C-2); 157.0; 160.0, 162.0 (C-6, C-8, CO). MS (DEI): 460 (M^+, 100); 388 (23); 174 (46). Anal. Calcd. for $C_{24}H_{28}N_8O_2$: C, 62.59; H, 6.13; N, 24.33. Found C, 63.75; H, 6.09; N, 24.25.

Ethyl 4-(N-4'-acetylphenylpiperazino)-8-dimethylaminopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate ***9c*** (67%); mp 249-250 °C. IR (KBr): 1710, 1660 (CO). ^1H NMR δ ($CDCl_3$): 1.45 (t, 3H, J = 7.1 Hz, CH_2CH_3); 2.50 (s, 3H, $COCH_3$); 3.31 (s, 3H, NMe_2); 3.41 (s, 3H, NMe_2); 3.59-3.69 (m, 6H, NCH_2); 4.50 (q, 2H, J = 7.1 Hz, CH_2O); 4.56-4.85 (m, 2H, NCH_2); 6.87, 7.91 (AA'XX' system, 4H, J = 8.8 Hz, $C_6H_4COCH_3$); 8.61 (s, 1H, H-2). MS (DEI): 489 (M^+, 15); 315 (30); 187 (42); 174 (100). Anal. Calcd. for $C_{24}H_{27}N_9O_3$: C, 63.00; H, 5.95; N, 27.55. Found C, 63.17; H, 6.02; N, 26.37.

Ethyl 8-dimethylamino-4-(4-piperidinopiperidino)pyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate ***9d*** (58%); mp 277-278 °C. IR (KBr): 1690 (CO). ^1H NMR δ ($CDCl_3$): 1.34 (t, 3H, J = 7.1 Hz, CH_2CH_3); 1.79-1.89 (m, 10H, CH_2); 2.07-2.18 (m, 8H, NCH_2); 3.26-3.33 (m, 7H, NMe_2, CH); 4.34 (q, 2H, J = 7.1 Hz, CH_2O); 8.63 (s, 1H, H-2). MS (FAB): 454 [$(MH)^+$, 100]; 408 (16). Anal. Calcd. for $C_{22}H_{31}N_9O_2$: C, 58.26; H, 6.89; N, 27.79. Found C, 58.47; H, 6.78; N, 27.86.

Ethyl 8-dimethylamino-4-piperazinopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxylate ***9e*** (66%); mp > 300 °C. IR (KBr): 2980, 1700 (CO). MS (FAB): 372 [$(MH)^+$, 12]; 237 (42); 197 (100) Anal. Calcd. for $C_{16}H_{21}N_9O_2$: C, 51.74; H, 5.70; N, 33.94. Found C, 51.61; H, 5.87; N, 33.83.

N-Propyl 8-dimethylamino-6-propylaminopyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine-3-carboxamide (9f):

A solution of **8** (0.10 g, 0.3 mmol) in propylamine (2 ml) was stirred at room temperature for 20 h. The solid formed was filtered off and recrystallized from $EtOH/CH_2Cl_2$ to afford **9f** (0.08 g, 74 %); mp 258-260 °C. IR (KBr): 3340 (NH); 3300 (NH); 1690 (CO). ^1H NMR δ ($CDCl_3$): 1.03 (t, 3H, J = 7.1 Hz, CH_2CH_3); 1.08 (t, 3H, J = 7.30 Hz, CH_2CH_3), 1.65-184 (m, 4H, CH_2CH_3); 3.37 (s, 3H, NMe_2); 3.45 (s, 3H, NMe_2); 3.53 (q, 2H, J = 6.20 Hz, NCH_2); 3.64 (q, 2H, J = 6.7 Hz, NCH_2); 7.34 (s, 1H, $NHCH_2$); 8.16 (s, 1H, NHCO); 8.71 (s, 1H, H-2). ^{13}C NMR δ ($CDCl_3$): 11.5, 11.6 (CH_2CH_3); 22.4, 23.0 (CH_2CH_3); 37.7 (NMe_2); 37.9 (NMe_2); 41.0, 43.0 (NCH_2); 108.7 (C-3); 118.9 (C-5a); 146.8, 147.7 (C-3a, C-9a) ;147.6 (C-2); 158.7, 161.3, 161.4(C-6, C-8, CO). MS (DEI): 447 (M^+, 14); 145 (40.4); 132 (100). Anal. Calcd. for $C_{16}H_{23}N_9O$: C, 53.77; H, 6.49; N, 35.27. Found C, 53.90; H, 6.59; N, 35.12.

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